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COMMENTARY

Sorting senescence, ageing, and ageism in the context of human reproduction

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Our collective fascination with aging in the realm of human reproduction continues unabated. And to start off the new year, *JARG* takes this Anthropocene seasoned topic to our readership in both familiar and unfamiliar landscapes as we delve into the biological, medical, societal, and ethical dimensions of the multifaceted problem of human fecundity. We begin our journey into the subject of reproductive aging by taking a comparative look at just how studies with model organisms have contributed to our understanding of the mechanisms leading to, through, and beyond an organisms' stage of reproductive competence.

Quesada-Candela and colleagues from the University of Pittsburgh tackle the problem of reproductive senescence in their review revealing along the phylogenetic pathway many of the widely conserved characteristics of the aging process between divergent and different eukaryotic models and allude to several relatively understudied processes with respect to human biology that are likely to attract more attention in the future (*Molecular basis of reproductive senescence: insights from model organisms;* https://doi.org/10.1007/s10815-020-01959). For example, the delicate balance between cell proliferation, the meiotic cell cycle, and cell death emerges a theme common to most of the species investigated to date. Similarly, mitochondria retain a center-stage role in the context of aging in both somatic and gametic cells and continue to be the target for anti-aging management within the expanding purview of human ARTs (see below).

Of the processes and mechanisms that have yet to receive a concerted research effort in mammalian systems—the unfamiliar if you will—are matters related to the management of protein stability and function (proteostasis as it is known), and not surprisingly the underpinnings of epigenetics have attracted great interest in lower animal models of cellular senescence as our readers will come to appreciate. Our continuing coverage of the traditional aspects of aging in the context of human ARTs examines the impact of advancing age on gamete quality (*Aging and ovarian stimulation modulate the relative levels of transcript abundance of oocyte DNA repair genes during the germinal vesicle-metaphase II transition in mice;* https://doi.org/10.1007/s10815-020-01981), embryo quality (*Treatment with Laevo (l)-carnitine reverses the mitochondrial function of human embryos*https://doi.org/10.1007/s10815-020-01973), and the more patient-centric concerns that we continue to be wary of given the societal imperative to delay child bearing (*Guidelines informing counseling on female age-related fertility decline: a systematic review*https://doi.org/10.1007/s10815-020-01967).

Along with the emphasis on reproductive aging itself, it appears timely to add to our conversation the concept of ageism given the importance ARTs and secondary commercial outlets have placed on enabling reproduction of our species outside the traditional boundaries of our reproductive lifespan. Ageism has reached new heights societally since Butler's original definition was proposed in 1969: *any form of stereotyping or discrimination on the basis of age*. Most frequently recognized as a matter pertaining to the elderly or those reaching later decades in the human scale of longevity, it need not be limited to those in advancing years but can and often does refer to restricted access or limiting resources in younger years as well—those not being of age yet.

For we reproductive specialists, as noted above, being preoccupied with ageism was early on seen to be a major issue in the context of a woman's fecundity. Not only were we focused on the waning chances of getting and sustaining pregnancy into the 4th decade, but the increased incidence of miscarriage or birth of children bearing certain genetic disorders (like Down syndrome), all became part and parcel of the hominid life spectrum delimiting career options that many women aspired to, commensurate with the introduction of safe and effective contraception. And once the ASRM gave its blessing to the "non-experimental nature" of egg freezing back in

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2013, it was off to the races taking the oocyte-based underpinnings of the maternal age effect into the hands of our expanding ART repertoire further enabling delayed childbearing.

Beyond the opportunities afforded by oocyte cryopreservation and egg donation, the aging problem with respect to our soma has taken on a new mechanistic focus aimed at the influence on the epigenome [1]. It is with this novel emphasis on epigenetics, and the emergent confluence with the role of the immune system that efforts to understand, harness, and manipulate cellular senescence have reached new heights, raising in tandem a new set of hopes [2]. Where will this new emphasis take reproductive medicine in the future?

The dominant driving force has for some time now been the realization of aging as related to an increase in meiotic errors in the oocyte [3]. And as noted above, although by apparently distinct mechanisms, when oocytes engage in their final "dance of the chromosomes" prior to fertilization, heightened chances of defective segregation are not limited to the doorstep approaching the end of the reproductive lifespan but also at the very beginning at puberty [4]. At least when considering what is behind the failure to efficiently segregate, the prevailing hypothesis over the years has been that the bioenergetic demands, whether for meiosis or mitosis, are not adequately met. Upon this profound *realization*, the finger pointing immediately shifted attention from the spindle-chromosome complex to mitochondrial metabolism [5].

Research into the oocentric and embryocentric metabolic underpinnings of genetic disasters linked to advancing maternal age has progressed notably over the past few years with exciting prospects on the horizon for rejuvenating the oocytes obtained from older women or those afflicted with premature ovarian insufficiency (POI) [6]. And the growing purview of the anti-aging movement is enlarging into domains such as fertility preservation [7]. As our specialty is well aware, we have a long history of attempts to sidetrack, remedy, rectify, or remediate whatever imperfections could be assigned as likely culprits in the egg aging conundrum and as efforts continue to focus on the oocyte, we should expect to witness more in the way of *nouveau* ARTs creeping into the repertoire made available for public consumption—hopefully without negative consequences on offspring produced.

In the larger scheme of aging, and as noted above, the contemporary approach is trending away from the *not-so-much card-carrying reductionist* aimed at the cell of interest (read oocyte), but rather works under the assumption that tissues and their dialog with the immune system rest at the heart of any individual cells' march into and through the senescence sojourn. Accordingly, the emphasis has shifted to the role of tissue macrophages and the concept of *inflammaging*, a way of thinking about the aging problem that originated nearly 15 years ago now [8, 9]. And only recently has it been implicated in the process of ovarian aging with the provocative link between the oocyte and its somatic environment awaiting elucidation [10].

In closing, with the New Year upon us, and hopes running high for the much-deserved turnaround from 2020, we at *JARG* would like to recognize the contributions of members of the Editorial Board who are leaving after many years of dutiful service. Our gratitude is extended to Richard Bronson, Michael Dahan, Eric Forman, Peter Hansen, Lin Liu, Nigel Pereira, and Marc-Andre Sirard. And with the changing of the guard arrives a new cadre of Board Members who begin their terms of service in 2021. Welcome to Debbie Blake, Giovanni Coticchio, Ariane Germeyer (another FIRBEE joins the team), Mary Mahony, Qing Sang, and Lei Wang, with each of you bringing to *JARG* a range of experiences and expertise that will strengthen our efforts going forward.

Stay tuned as next month, our emphasis on reproductive genetics will be accompanied by several new technological breakthrough contributions. Happy 2021!

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